THE CHRONIC TOXICITY OF TRICHLOROETHYLENE: A STUDY * † ‡

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DURING recent years trichloroethylene has found increasing use as an analgesic drug. Acute changes in metabolism following its employment for short periods of time have been shown to be minimal (1–3). However, in the toxicological literature case reports are found of industrial poisoning by this drug, with neurological and hepatorenal sequelae (4–5). Such complications have occurred in employees working every day over a period of several months in atmospheres contaminated with low concentrations of the vapor. These conditions may be found in dry cleaning and in metallurgical processing plants. Previous reports have postulated "chemical impurities" or degradation products of trichloroethylene as the cause of the toxic manifestations. Such abnormal constituents may be found in concentrations as high as 5 per cent in the commercial preparations.

For medical use trichloroethylene is supplied as a chemically purified preparation. It can be decomposed partially in the presence of soda lime, either by a direct chemical reaction with the hydroxide or by the heat generated during the carbon dioxide neutralization, to form toxic dichloracetylene. Accordingly, employment of soda lime is contraindicated in the presence of trichloroethylene vapor.

In order to ascertain whether the chemically purified preparation of this drug used without soda lime has chronic adverse effects, animals were subjected to prolonged exposure, under conditions simulating chronic exposure of human beings. At the termination of the experiment, functional tests of the major organ systems were made and the animals then subjected to postmortem examinations.

METHOD

An animal cage was designed in which trichloroethylene vapor of known concentrations could be provided for prolonged periods with-

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out accumulation of excessive carbon dioxide and water vapor (fig. 1). Washed air was passed through an ordinary anesthetic, wick-type vaporizer into the cage at a rate of approximately 50 liters per minute. This cage was airtight, and had an exhaust vent at the corner opposite the vaporizer. Vapor concentrations of trichloroethylene were determined periodically (2) through this exhaust vent, and were maintained between 0.05 and 0.1 volumes per cent. This is approximately 100 to 500 times the concentration that would be encountered as an industrial air contaminant. One dog, 3 rabbits and 3 rats were maintained on chronic exposure to this concentration of the drug for a test period of ninety days. The exposures averaged eighteen hours per day,

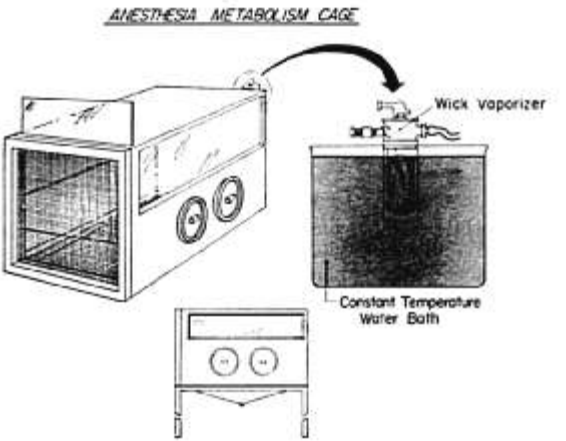

FIG. 1. Cage in which animals were exposed to trichloroethylene vapor. Enlargement above shows the anesthetic wick vaporizer employed to obtain concentrations.

being interrupted only for feeding and cleaning purposes, and by personnel limitations.

Bromsulphalein and thymol turbidity tests for liver function and the phenolsulfonphthalein test for renal function were done on the dog and rabbits before and immediately after exposure. Microscopic examination of urine sediment and tests for protein were similarly performed. Erythrocyte, leukocyte and hemoglobin values were determined on all animals before and after exposure.

The rats were half grown animals sixty-five days old; their growth rate was compared with a group of 6 control animals of the same age and maintained on a similar diet. The rats and rabbits were sacrificed at the termination of the exposure and the dog was autopsied

three months later. Gross and microscopic observations were made of the following tissues: heart, lung, liver, kidney, adrenal, central nervous system, pancreas, spleen, striated muscle, esophagus, stomach, salivary gland, trachea, autonomic ganglia, bone marrow, thyroid and lymph nodes.

RESULTS

During the exposure the animals were somewhat sluggish in their reactions and appeared to spend much time sleeping. Painful stimuli induced only a slight withdrawal response. However, they ate and drank with their usual facility. Responsiveness to auditory stimuli was grossly normal. When first removed from the cage, the animals appeared unsteady on their feet and moved with uncertainty. Locomotion became normal within fifteen minutes.

GROWTH RATE

The test animals gained an average of 6 per cent more than the controls. This difference was not statistically significant, but did indicate that normal food intake and growth rate were maintained.

LIVER FUNCTION

Thymol turbidity tests were normal in all the animals tested, both before and after exposure. The bromsulphalein results were normal in the rabbits, but the dog showed a 6 per cent dye retention immediately following exposure. However, a repetition of this test five days later revealed no retention. Liver function was therefore considered not to be significantly altered.

RENAL FUNCTION

Urinalyses in the rabbits and dog following exposure showed no unusual formed elements and no protein. Phenolsulfonphthalein tests were done on these animals during the first week after removal from the cage. One cubic centimeter of dye was administered intravenously and urine was collected for two hours afterward. Fifty per cent excretion was considered to be within normal range. According to this standard, renal function was normal in all the animals tested. Although these are admittedly crude tests of renal efficiency, it was considered that significant renal dysfunction did not develop during the exposure.

HEMATOPOIETIC FUNCTION

Erythrocyte and leukocyte counts and hemoglobin determinations done on all the animals following exposure showed no remarkable alteration when compared with the values obtained originally. Abnormal cells were not seen in the blood of any of the animals. No indirect evidence was found of interference with function of bone marrow.

ANATOMIC STUDIES

All animals appeared well nourished. The lungs of one rabbit revealed suppurative bronchopneumonia and small focal hepatic abscesses. This inflammatory process was interpreted as being unrelated to the experimental procedure. A slight focal encephalitis of the type that is endemic in the stock of rabbits used was encountered in one other animal. Otherwise, the animals were free of gross or microscopic lesions. There was no evidence of old or recent cellular injury to parenchymatous tissues. The nervous systems were free of degenerative changes, and the hematopoietic tissues were normally active and full.

SUMMARY

One dog, 3 rabbits and 3 rats were exposed continuously to trichloroethylene vapor in concentrations of 0.05 to 0.1 volumes per cent for periods averaging eighteen hours daily over a three month interval. This prolonged exposure produced no observable functional or anatomic adverse effects.

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